Title	Liver fibrosis index is associated with functional outcome among acute ischemic stroke patients
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Citation	Journal of Stroke and Cerebrovascular Diseases , 33 (2) : 107537
Issue Date	2023-12-29
DOI	
Self DOI	
URL	https://ir.lib.hiroshima-u.ac.jp/00056132
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Relation	

Title Page

Full title of the manuscript:

Liver fibrosis index is associated with functional outcome among acute ischemic stroke patients.

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Funding

This study was supported by a research grant from the Japan Society for the Promotion of Science KAKENHI (grant numbers 20K16579, 21K10210, 21K11214, and 23H02827) and Honjo International Scholarship Foundation.

Conflicts of interest/Competing interests

Dr. Maruyama received Grants-in-Aid for Scientific Research (23H02827) and research support from Eisai, Takeda Pharmaceutical, Otsuka Pharmaceutical, Nihon Pharmaceutical, Shionogi, Teijin Pharma, Fuji Film, Sumitomo Pharma, Nihon Medi-Physics, Daiichi Sankyo, Kyowa Kirin, Sanofi, Novartis, Tsumura, Japan Blood Products Organization, Chugai Pharmaceutical, Mitsubishi Tanabe Pharma, and Viatris, which are unrelated to the submitted work.

All other authors declare that they have no conflicts of interest.

Shortened version of the title

Ischemic stroke outcome and liver fibrosis index

Key words

FIB-4 index; FIB-5 index; Ischemic stroke; Outcome.

Abstract

Introduction: The fibrosis-4 (FIB-4) index and the fibrosis-5 (FIB-5) index are noninvasive markers of liver fibrosis in patients with nonalcoholic fatty liver disease. Although liver fibrosis a potential risk factor for stroke development, it is uncertain whether liver fibrosis influences stroke outcomes. We investigated the associations between these two indices and stroke patient outcomes and compared their predictive accuracy.

Methods: We conducted a double-center, hospital-based, retrospective study. Consecutive acute ischemic stroke patients (n=2399) were analyzed. We calculated the FIB-4 index and the FIB-5 index and evaluated their relationships with poor stroke outcome, which was defined as a modified Rankin Scale score of 3–6 at three months after stroke. We evaluated the ability of each index to predict stroke outcome according to cutoff values calculated from receiver operating characteristic (ROC) curves.

Results: Of 2399 recruited patients, 1549 patients (mean age, 73 years) were analyzed. The FIB-4 index and FIB-5 index had similar areas under their ROC curves for predicting stroke outcome (FIB-4 index, 0.675 and FIB-5 index, 0.683, P=0.334). The cutoff points of the FIB-4 index and FIB-5 index according to the ROC analysis were associated with

poor stroke outcome in the multivariable analyses (odds ratio [OR] 2.23, 95% confidence interval [CI] 1.72–2.89, OR 1.93, 95% CI 1.47–2.54, respectively).

Conclusions: Liver fibrosis scores may be useful for predicting outcomes in patients with acute stroke. The FIB-4 and FIB-5 indices should be considered comprehensive tools for assessing the outcome risk after ischemic stroke.

Introduction

Nonalcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis, as determined by either imaging or histology, and is associated with metabolic factors. Some 10-20% or more of NAFLD patients have nonalcoholic steatohepatitis (NASH), a condition associated with hepatocellular damage and inflammation[1]. The prevalence of NAFLD is increasing worldwide, particularly in developed countries, and is expected to rise in the future[2].

NASH has gained attention as a potential risk factor for the development of atherosclerosis, cardiovascular disease, and stroke[3], but the association between NASH and the occurrence of stroke is still debated[4]. In addition, it is uncertain whether liver fibrosis influences stroke outcomes.

In clinical practice, it is challenging to perform abdominal ultrasonography or liver biopsies on every patient. The fibrosis-4 (FIB-4) index, which is calculated from age, aspartate aminotransferase (AST) concentration, alanine aminotransferase (ALT) concentration, and platelet count, is a noninvasive and widely used marker of liver fibrosis in patients with NAFLD[5]. The FIB-4 index has been utilized for the prediction of hospital mortality in patients with acute coronary syndrome and for risk categorization of

heart failure and major bleeding after discharge[6]. The FIB-4 index has been associated with clinical outcomes among patients with heart failure[7]. For acute ischemic stroke patients who undergo thrombolysis, the FIB-4 index is useful for predicting symptomatic intracerebral hemorrhage, mortality, and poor stroke outcomes[8,9]. The fibrosis-5 (FIB-5) index, which is calculated from albumin, alkaline phosphatase (ALP), AST-to-ALT ratio, and platelet count, was proposed as another simple liver fibrosis marker[10]. Several studies have shown that the FIB-5 index better predicts the outcome of patients with heart failure than the FIB-4 index[11].

In this study, we investigated the associations of these two indices with stroke patient outcomes and compared their accuracy at predicting stroke outcomes.

Methods

Study design and patients

We conducted this double-center, hospital-based, retrospective study in consecutive patients with acute ischemic stroke hospitalized at Hiroshima University Hospital and Chikamori Hospital. The study followed the Declaration of Helsinki and was approved by the ethics committees at Hiroshima University, including the institutional review

board (approval number E–856).

All patients with ischemic stroke who were admitted to our institutes within seven days of symptom onset or who were last known well were prospectively registered in our registry. Data from October 2009 to September 2018 were retrospectively reviewed, and patients who met the following criteria were included: 1) admitted with acute ischemic stroke and 2) had available medical history and laboratory data on admission. Even if the symptoms disappeared within 24 hours, the patient was registered in the database as having an ischemic stroke if new infarct regions were found on head imaging examination.

Clinical data collection

The baseline data on the following variables were collected from the registry: age, sex, body mass index (BMI), daily alcohol intake (>40g), and medical history, such as hypertension, dyslipidemia, diabetes mellitus (DM), atrial fibrillation (Af), chronic kidney disease (CKD), ischemic heart disease, and stroke.

Hypertension, dyslipidemia, DM, Af, CKD, and ischemic heart disease were previously defined[12]. Stroke was the comprehensive term for ischemic stroke, transient ischemic stroke, hemorrhagic stroke, and subarachnoid hemorrhage.

Furthermore, we included data such as the premorbid modified Rankin scale (mRS), National Institutes of Health stroke scale (NIHSS) on admission, stroke etiology, acute reperfusion therapy, and laboratory findings (hemoglobin, platelet, AST, ALT, ALP, cholinesterase (ChE), albumin, total cholesterol, C-reactive protein (CRP), and estimated glomerular filtration rate (eGFR)). Most blood sample were collected at admission. If samples could not be obtained on admission, we collected them within two days after admission. The formulas for FIB-4 index[5] and FIB-5 index[10] are as follows.

FIB-4 index：(Age×AST (IU/L))/(Platelet (10^9/L)×√ALT (IU/L))

FIB-5 index：(Alb (g/L)×0.3 + Platelet (10^9/L)×0.05) −(ALP (U/L)×0.014 +(AST/ALT) ×6 +14)

The FIB-4 value is generally classified into three groups: low (<1.30), intermediate (1.30–2.67), and high (>2.67). The high-risk group has a positive predictive value of 80% for advanced liver fibrosis, and the low-risk group has a negative predictive value of 90% for advanced liver fibrosis[13]. We divided our overall patient population into these three groups. ALP was measured using the Japan Society of Clinical Chemistry (JSCC) method. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method is used worldwide for ALP catalytic concentration measurement. When the IFCC

method is used, the human blood ALP activity is approximately one-third of the JSCC method's activity[14]. In the present study, we calculated the FIB-5 index after conversions of the ALP values (IFCC) from those (JSCC) in the regression formulas for humans[14] (y [IFCC]= 0.337x [JSCC] + 2.959).

The mRS and NIHSS scores were defined as described[15,16]. The stroke etiology was classified by stroke neurologists according to the Trial of ORG 10172 in the Acute Stroke Treatment criteria[17].

Assessment of stroke outcome

The stroke outcome was evaluated as the three-month functional status. We assessed a good outcome as a score of 0–2 on the mRS and a poor outcome as a score of 3–6. Essentially, attending physicians evaluated the mRS score at three months after stroke onset by examining each patient. When the physicians could not examine a patient, they assessed the mRS score based on a review of the medical records or by contacting the patient's caregiver.

Statistical analyses

All patient data were analyzed using the Mann–Whitney *U* test for continuous data and the two-sided Fisher's exact test for categorical data. Continuous variables are given as the median [interquartile range]. Categorical variables are given as frequencies and percentages. Receiver operating characteristic (ROC) curves were drawn to obtain the cutoff values for the FIB-4 index and FIB-5 index as factors predicting outcome, and the area under the curve (AUC) for each index to predict a good outcome (mRS score of 0–2 at three months) was calculated.

Multivariable logistic analysis was performed to identify the predictors of good stroke outcome from among the baseline characteristics, including age, sex, body mass index, daily alcohol intake, comorbidities (hypertension, dyslipidemia, DM, CKD and Af), previous stroke, previous ischemic heart disease, and NIHSS, FIB-4 index, and FIB-5 index, with a backward selection procedure using $P>0.10$ of the likelihood ratio as the exclusion criterion (Model 1). Age was excluded from the variables (**Table 3**) since it is included in the FIB-4 index. For Model 2, other blood laboratory findings (hemoglobin, ALP, ChE, albumin, total cholesterol, and CRP) were added to the indicators in Model 1. Albumin and ALP were excluded from the variables (**Table 4**) since these values were included in the FIB-5 index. Significance was defined as

$P<0.05$ for all tests. All analyses were performed using JMP 14.0.0 statistical software (SAS Institute Inc., Cary, NC, USA).

Results

The flow chart of patient selection is shown in **Fig. 1**. A total of 2399 acute ischemic stroke patients were enrolled in the registry from October 2009 to September 2018. Of these, 17 patients were excluded due to a lack of data on premorbid mRS, 429 patients due to a preexisting disability with an mRS ≥3, 401 patients due to a lack of data on their stroke outcomes at three months, and 3 patients due to a lack of data on factors consisting of the FIB-4 index (**Fig. 1**). Finally, 1549 patients were analyzed. Among them, 997 patients (64.3%) were living independently at three months after stroke onset. The baseline characteristics of the patients with mRS 0–2 and those with mRS 3–6 are shown in **Table 1**. The patients with good outcomes (mRS 0–2) were younger, had higher BMI, and had lower NIHSS scores on admission. This group had a greater percentage of patients with preexisting dyslipidemia but fewer with Af, CKD, or stroke. There were significant differences in the laboratory values between patients with good outcomes and those without. In addition, the patients with good outcomes had a lower

FIB-4 index (1.89 vs. 2.62, *P*<0.001) and a higher FIB-5 index (-0.15 vs. -3.22, *P*<0.001).

Associations between FIB-4 index, baseline characteristics and stroke outcomes

The 1549 patients (mean age: 73±12 years) were divided into three groups of FIB-4 score: low risk (n=282, 18.2%), intermediate risk (n=755, 48.7%) and high risk (n=512, 33.1%). The associations between the FIB-4 index and baseline characteristics are shown in **Table 2**. A high FIB-4 index was associated with a higher frequency of female sex, hypertension, Af, ischemic heart disease, and CKD and with a lower frequency of dyslipidemia and DM. Multivariable analysis showed that a high FIB-4 index was independently associated with poor functional outcome after adjusting for sex, BMI, daily alcohol intake, comorbidities and NIHSS (odds ratio (OR) 1.89, 95% confidence interval (CI) 1.44–2.48, *P*<0.001, **Table 3**, Model 1). A high FIB-4 index was also associated with poor outcome even after considering other laboratory findings (OR 1.71, 95% CI 1.27–2.29, *P*<0.001, **Table 3**, Model 2). The optimal cutoff of the FIB-4 index to predict poor outcome was ≥2.44, which had a sensitivity of 70%, a specificity of 58%, and an AUC of 0.675 (**Fig. 2A**). Values above this cutoff were also associated

with poor stroke outcomes in the multivariable analysis. On the other hand, the FIB-4 index (continuous range) was not associated with outcome after adding other laboratory findings on top of the first set of variables. Although the FIB-4 index already includes age as one of its components, additional analyses were conducted to further account for the effects of age. The FIB-4 index (ROC cutoff value) was also associated with stroke outcomes in the multivariable analysis when adding age to the selected variables as determining factors for outcomes. A high FIB-4 index tended to be associated with poor functional outcomes, although the FIB-4 index (continuous range) was not associated with outcomes (**Supplemental Table 1**).

The associations between FIB-5 index, FIB-4 index and stroke outcomes

The FIB-5 index exhibited a notably strong negative correlation with the FIB-4 index. (Spearman's correlation analysis, ρ -0.835, $P<0.001$). The optimal cutoff of the FIB-5 index to predict poor outcome was ≤-2.41, which had a sensitivity of 70%, a specificity of 58%, and an AUC of 0.683 (**Fig. 2B**). There was no difference between the AUC of the FIB-4 index and that of the FIB-5 index ($P=0.334$). Values below this cutoff were associated with poor stroke outcomes in the multivariable analysis (**Table**

4). The FIB-5 index (continuous range) was also associated with poor stroke outcome (**Table 4**).

Associations between FIB-4 index, FIB-5 index and stroke outcomes for patients without daily alcohol intake

Of 1549 patients, 457 patients with daily alcohol intake were excluded. The patients with good outcomes (n=658) had a lower FIB-4 index (1.94 vs. 2.68, $P<0.001$) and a higher FIB-5 index (-0.49 vs. -3.47, $P<0.001$) than those with poor outcomes (n=406). The optimal cutoff of the FIB-4 index to predict poor outcome was ≥2.44, which had a sensitivity of 68%, a specificity of 60%, and an AUC of 0.667. The optimal cutoff of the FIB-5 index to predict poor outcome was ≤-3.36, which had a sensitivity of 76%, a specificity of 52%, and an AUC of 0.682. FIB-4 index ≥2.44 was independently associated with poor stroke outcomes (OR 2.13, 95% CI 1.56–2.88, $P<0.001$). FIB-5 index ≤-3.36 was also independently associated with poor stroke outcomes (OR 2.27, 95% CI 1.65–3.12, $P<0.001$).

Discussion

Liver fibrosis markers such as the FIB-4 index and FIB-5 index were associated with stroke outcome. The predictive powers of the FIB-4 index and FIB-5 index using ROC analysis for stroke outcomes were almost the same. These indices might be promising markers to predict stroke outcomes.

NASH, characterized by liver inflammation and fibrosis in the absence of significant alcohol consumption, has gained attention as a potential risk factor for the development of atherosclerosis and the incidence of myocardial infarction[3,18]. In addition, NASH has been associated with the presence of Af [19,20]. Hence, these risk factors, including atherosclerotic and cardioembolic factors, might be linked via liver fibrosis to the incidence of ischemic stroke. Several studies have investigated the association between NASH and stroke, providing valuable insights into this relationship. Three studies using the FIB-4 index to diagnose liver fibrosis showed that this index was useful for predicting the incidence of stroke[21-23]. A recent meta-analysis of 18 studies with 17031672 participants showed that nonalcoholic fatty liver disease was associated with an increased risk of stroke (OR 1.18, 95% CI: 1.08–1.30, P=0.0005) [24]. These results may suggest the importance of early detection of liver fibrosis and intervention for stroke prevention.

Evidence is growing of the association between liver fibrosis and the onset of stroke, but there are limited reports of an association between liver fibrosis and the outcome of stroke. Fandler-Höfler S et al. evaluated the incidence of severe liver fibrosis using the FIB-4 index and the influence of liver fibrosis on stroke outcomes among 414 acute consecutive ischemic stroke patients[25]. The rates of severe liver fibrosis (FIB-4 index >2.67) were lower than those of our cohort (22.2% vs. 33.1%) because our cohort was older than theirs (73 years vs. 70.2 years). They found that severe liver fibrosis was independently associated with the presence of Af; however, the FIB-4 index was not associated with stroke outcomes after adjusting for age and stroke severity. In our study, age was excluded as an adjustment factor in the multivariable analysis since the FIB-4 index includes an age component. The FIB-4 index (continuous range) was not associated with stroke outcomes in the multivariable analysis with age (**Supplemental Table 1**). Therefore, it is important to be cautious when interpreting the effect of the FIB-4 index on stroke incidence or outcomes, and attention should be paid as to whether age is adjusted for. It might be necessary to explore liver fibrosis markers that do not incorporate the factor of age. Several reports have suggested associations between FIB-4 index and hemorrhage expansion after primary intracranial hemorrhage (ICH)[26,27] and symptomatic

ICH after intravenous thrombolysis[9]. Possible mechanisms between hemorrhagic complications and liver fibrosis may include coagulopathy, endothelial dysfunction, and vascular inflammation[27]. Although we could not evaluate the hemorrhagic complications in our cohorts, recurrence stroke not only ischemic but also hemorrhagic might influence the poor stroke outcomes.

The novelty of this study was the evaluation of the FIB-5 index for stroke outcomes because the FIB-5 index has also been proposed as an indicator of liver fibrosis[10]. Age, as a component of the FIB-4 index, was not included in FIB-5 index, but additional factors such as ALP and albumin were included. The predictive power of the FIB-5 index to predict stroke outcomes was similar to that of the FIB-4 index. In addition, the FIB-5 index was associated with poor stroke outcomes even after adjustment for various factors, including age. Hence, the FIB-5 index might reflect liver fibrosis independently of age and could accurately predict stroke outcome. Since the FIB-5 index includes ALP and albumin, it might reflect not only liver fibrosis but also other phenomena that contribute to stroke outcome. Serum ALP is usually used as a marker of liver disease or liver fibrosis. ALP is also elevated in those who are at high risk of having a stroke and is associated with atherosclerosis, which includes vascular calcification[28]. In addition, ALP is elevated

in patients who develop acute ischemic stroke as a result of disruption of the blood brain barrier and neuroinflammation[29]. Indeed, there has been accumulating evidence about ALP as a prognostic stroke biological marker[30-32]. Lower albumin is associated with not only liver dysfunction but also systemic inflammation and malnutrition, as well as with poor outcomes in patients with stroke[33,34]. Therefore, the FIB-5 index might be evaluated as a comprehensive index that reflects atherosclerosis, systemic inflammation, and nutritional status, rather than as an indicator of liver fibrosis alone. Further investigation is needed to determine whether ultrasonographic assessment of liver fibrosis is associated with stroke outcome.

There are several limitations to this study. First, this is a retrospective cohort study conducted at two sites, so our findings have limited generalizability. Second, it was difficult to assess every patient's condition reliably and in detail three months after onset because many patients were hospitalized elsewhere for rehabilitation. For this reason, there was a deficit in mRS data at three months. Although the number of cases was reduced at three months, the data from the 1549 patients may provide a useful perspective. Third, for the definition of NAFLD, the upper limit of alcohol drinking is 30 g/day in males and 20 g/day in females[1]. We collected the data as the daily alcohol intake (>40

g/day) based on the medical records at each institution. Although the liver fibrosis markers were associated with stroke outcome among acute ischemic stroke patients after excluding the patients with daily alcohol intake, it might be noted that our results are not based on the stringent criteria for NAFLD. Fourth, we could not collect whether the patients had a medical history of hepatitis (i.e., viral hepatitis, hemochromatosis, or autoimmune hepatitis). This study may include factors other than liver fibrosis due to NASH/NAFLD. Finally, we calculated the FIB-5 index based on ALP values (IFCC). Several studies considering the FIB-5 index might have used the ALP values (JSCC)[7, 35]. Therefore, we should carefully discuss and compare the cutoff points of the FIB-5 index across different studies.

Conclusion

Liver fibrosis scores may be useful for predicting outcome in patients with acute stroke. No difference in predictive value was found between the FIB-4 index and the FIB-5 index. These two indices may be affected by age, arteriosclerosis, and nutritional status in addition to liver fibrosis and should be considered as a comprehensive tool for assessing outcome risk after ischemic stroke.

Acknowledgments

None.

Figure legends

Figure 1. Patient selection process

Patients were excluded for a premorbid mRS ≥3 (n=429), lack of data on mRS (n=17), lack of stroke outcome at three months (n=401), and lack of data making up the FIB-4 index (n=3).

Abbreviations; FIB-4 index, fibrosis–4 index; mRS, modified Rankin Scale.

Figure 2. The area under the curve of the modified Rankin Scale for the two liver fibrosis indices

A: The AUC of mRS 0–2 for the FIB-4 index was 0.675 (sensitivity: 0.70, specificity: 0.583).

B: The AUC of mRS 0–2 for the FIB-5 index was 0.683 (sensitivity: 0.70, specificity: 0.579).

Abbreviations; AUC, area under the curve; FIB-4 index, fibrosis-4 index; FIB-5 index, fibrosis-5 index, mRS: modified Rankin Scale.

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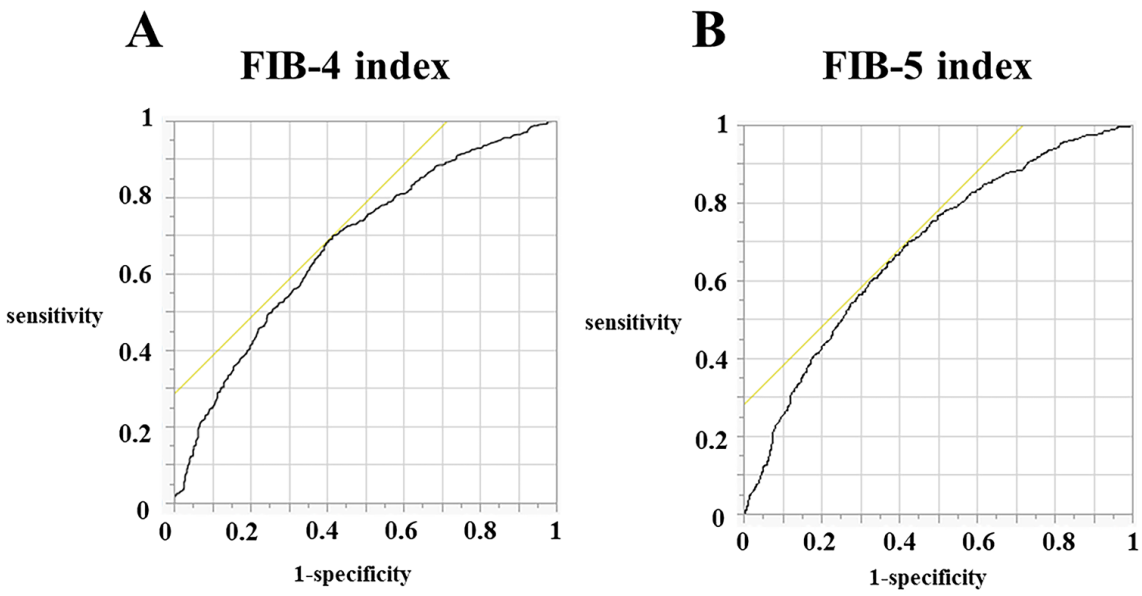

1 **AUC：0.675** **AUC：0.683**

Table 1. Comparisons between the patients with three-month modified Rankin Scale scores of 0–2 in the cohort.

Variables	mRS at three months		
	0–2 (n=997)	3–6 (n=552)	*P*
Background			
Female	328 (32.9)	249 (45.1)	<0.001
Age (years)	72 [64, 79]	79 [70, 85]	<0.001
BMI (kg/m^2) (n=1528)	23.1 [21.2, 25.6]	22.2 [20.0, 24.5]	<0.001
Daily alcohol intake (n=1521)	326 (33.1)	131 (24.4)	<0.001
Medical History			
Hypertension	687 (68.9)	391 (70.8)	0.454
Dyslipidemia (n=1546)	516 (51.8)	253 (46.1)	0.034
Diabetes mellitus (n=1548)	352 (35.3)	187 (33.9)	0.616
Atrial Fibrillation (n=1548)	165 (16.6)	174 (31.6)	<0.001
Ischemic heart disease	126 (12.6)	86 (15.6)	0.123
Chronic kidney disease	354 (35.5)	259 (46.9)	<0.001
Stroke (n=1548)	251 (25.2)	174 (31.5)	0.009
Stroke severity and subtype			
NIHSS on admission (n=1513)	2 [1, 4]	8 [3, 17]	<0.001
Subtype for ischemic stroke			<0.001
Atherothrombotic infarction	250 (25.1)	114 (20.7)	
Cardioembolic stroke	220 (22.1)	195 (35.3)	
Lacunar	289 (29.0)	111 (20.1)	
Other etiology	238 (23.9)	132 (23.9)	
Acute reperfusion therapy			
rt-PA, MT	13 (1.3)	20 (3.6)	0.005
Laboratory findings			
Hb (g/dL)	13.8 [12.4, 15.1]	13.1 [11.5, 14.5]	<0.001
Platelet (10^4/μL)	19.9 [16.1, 23.9]	18.1 [14.6, 22.5]	<0.001
AST (IU/L)	22 [19, 28]	24 [20, 34]	<0.001
ALT (IU/L)	18 [14, 26]	17 [12, 25]	0.009

ALP (IU/L) (IFCC method) (n=1513)	81 [66, 100]	89 [70, 109]	<0.001
ChE (IU/L) (n=1479)	294 [241, 343]	251 [202, 315]	<0.001
Alb (g/dL) (n=1539)	4.2 [3.9, 4.4]	3.9 [3.5, 4.2]	<0.001
Total Cholesterol (mg/dL) (n=1538)	191 [166, 221]	184 [157, 216]	0.009
eGFR (mL/min./1.73m^2) (n=1544)	68.2 [52.9, 82.4]	61 [47.6, 80.1]	<0.001
CRP (n=1541)	0.16 [0.1, 0.4]	0.3 [0.1, 1.2]	<0.001
Liver Fibrosis marker			
FIB-4 index	1.89 [1.34, 2.65]	2.62 [1.88, 3.74]	<0.001
FIB-5 index (n=1504)	-0.15 [-3.03, 2.91]	-3.22 [-6.90, -0.11]	<0.001

Note: Data are presented as the number (%) or median [interquartile range].

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ChE, cholinesterase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; FIB-4 index, fibrosis-4 index; FIB-5 index, fibrosis-5 index; Hb, hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator.

Table 2. Comparisons between FIB-4 strata.

Variables	FIB-4 index (n=1549)			
	Low (n=282)	Intermediate (n=755)	High (n=512)	*P*
Background				
Female	86 (30.5)	263 (34.8)	228 (44.5)	<0.001
BMI (kg/m^2) (n=1528)	23.5 [21.3, 26.2]	23.1 [21.0, 25.5]	22.3 [20.0, 24.6]	<0.001
Prestroke mRS	0 [0, 1]	0 [0, 1]	1 [0, 1]	<0.001
Alcohol consumption (n=1521)	100 (36.2)	233 (31.2)	124 (24.9)	0.003
Medical History				
Hypertension	183 (64.9)	530 (70.2)	365 (71.3)	0.152
Dyslipidemia (n=1546)	170 (60.5)	389 (51.5)	210 (41.2)	<0.001
Diabetes mellitus (n=1548)	117 (41.5)	276 (36.6)	146 (28.6)	<0.001
Atrial Fibrillation (n=1548)	23 (8.2)	149 (19.7)	167 (32.7)	<0.001
Ischemic heart disease	17 (6.0)	107 (14.2)	88 (17.2)	<0.001
Chronic kidney disease	77 (27.3)	264 (35.0)	272 (53.1)	<0.001
Stroke (n=1546)	66 (23.4)	219 (29.0)	140 (27.4)	0.198
Stroke severity and subtype				
NIHSS on admission (n=1510)	2 [1, 4]	3 [1, 5]	4 [2, 13]	<0.001
Subtype for ischemic stroke				<0.001

Atherothrombotic infarction	78 (27.7)	207 (27.4)	79 (15.4)	
Cardioembolic stroke	34 (12.1)	178 (23.6)	203 (39.7)	
Lacunar	94 (33.3)	205 (27.2)	101 (19.7)	
Other etiology	76 (27.0)	165 (21.9)	129 (25.2)	
Acute reperfusion therapy				
rt-PA, MT	5 (1.8)	17 (2.3)	11 (2.2)	0.89
Laboratory findings				
Hb (g/dL)	14.2 [12.6, 15.5]	13.8 [12.3, 15.1]	13.1 [11.6, 14.2]	<0.001
ALP (IU/L) (n=1513)	81 [65, 101]	84 [68, 104]	85 [67, 106]	0.119
ChE (IU/L) (n=1476)	323 [259, 380]	294 [245, 340]	239 [195, 292]	<0.001
Alb (g/dL) (n=1539)	4.2 [3.9, 4.5]	4.1 [3.8, 4.4]	4.0 [3.6, 4.3]	<0.001
Total Cholesterol (mg/dL) (n=1538)	202 [171, 230]	193 [167, 222]	178 [151, 204]	<0.001
eGFR (mL/min./1.73m^2) (n=1544)	74.1 [59, 88.3]	68.9 [53.6, 82.7]	58.8 [44.4, 71.5]	<0.001
CRP (n=1541)	0.2 [0.1, 0.5]	0.2 [0.1, 0.4]	0.2 [0.1, 0.9]	<0.001
Outcome				
mRS 0–2 at 3 months	232 (82.3)	522 (69.1)	243 (47.5)	<0.001
mRS 6 at 3 months	7 (2.5)	22 (2.9)	60 (11.7)	<0.001

Note: Data are presented as the number (%) or median [interquartile range].

Abbreviations: Alb, albumin; ALP, alkaline phosphatase; BMI, body mass index; ChE, cholinesterase; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator.

Table 3. Odds ratio for poor functional outcome at 3 months by the FIB-4 index

	ROC cutoff value	***P***	**high vs. low or intermediate**	***P***	**continuous range, 1-point increase**	***P***
Model 1	2.23 (1.72–2.89)	<0.001	1.89 (1.44–2.48)	<0.001	1.11 (1.03–1.20)	0.003
Model 2	2.08 (1.57–2.76)	<0.001	1.71 (1.27–2.29)	<0.001	1.04 (0.98–1.13)	0.184

Model 1: FIB-4 index, sex, body mass index, daily alcohol intake, comorbidities (hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease and atrial fibrillation), previous stroke, previous ischemic heart disease, and NIHSS on admission. Age was excluded from the variables since the effect of age was included in the FIB-4 index.

Model 2: Other blood laboratory findings (hemoglobin, ALP, ChE, albumin, total cholesterol, and CRP) were added to Model 1.

Abbreviations: ALP, alkaline phosphatase; ChE, cholinesterase; CRP, C-reactive protein; FIB-4 index, fibrosis-4 index; NIHSS, National Institute Health Stroke Scale; ROC, receiver operating characteristic.

Table 4. Odds ratio (95% CI) for poor functional outcome at 3 months by FIB-5 index

	ROC cutoff value	*P*	continuous range, 1-point decrease	*P*
Model 1	1.93 (1.47–2.54)	<0.001	1.05 (1.03–1.08)	<0.001
Model 2	1.73 (1.29–2.32)	<0.001	1.05 (1.02–1.07)	0.002

Model 1: FIB-5 index, age, sex, body mass index, daily alcohol intake, comorbidities (hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease and atrial fibrillation), previous stroke, previous ischemic heart disease, and NIHSS on admission.

Model 2: Other blood laboratory findings (hemoglobin, ChE, total cholesterol, and CRP) were added to Model 1. Platelet, ALP, and albumin were excluded from the variables since those laboratory findings were included in the FIB-5 index.

Abbreviations: ALP, alkaline phosphatase; ChE, cholinesterase; CRP, C-reactive protein; FIB-5 index, fibrosis-5 index; NIHSS, National Institute Health Stroke Scale; ROC, receiver operating characteristic.

Supplemental Table 1. Odds ratio for poor functional outcome at 3 months by the FIB-4 index

	ROC cutoff value	*P*	high vs. low or intermediate	*P*	continuous range, 1-point increase	*P*
Model 1	1.58 (1.18–2.10)	0.002	1.38 (1.03–1.85)	0.030	1.04 (0.99–1.11)	0.111
Model 2	1.52 (1.13–2.04)	0.006	1.30 (0.96–1.77)	0.089	1.02 (0.97–1.08)	0.434

Model 1: FIB-4 index, age, sex, body mass index, daily alcohol intake, comorbidities (hypertension, dyslipidemia, diabetes mellitus, chronic kidney disease and atrial fibrillation), previous stroke, previous ischemic heart disease, and NIHSS on admission.

Model 2: Other blood laboratory findings (hemoglobin, ALP, ChE, albumin, total cholesterol, and CRP) were added to Model 1.

Abbreviations: ALP, alkaline phosphatase; ChE, cholinesterase; CRP, C-reactive protein; FIB-4 index, fibrosis-4 index; NIHSS, National Institute Health Stroke Scale; ROC, receiver operating characteristic.